terms of the cortico-ponto-cerebellar pathway or through the inferior cerebellar peduncle via climbing fibres from the olive in terms of the cortico-rubro-olivo-cerebellar pathway [4]. The cerebellum projects to multiple cerebral areas. One of the main cerebellar efferent pathways consists of projections from the cerebellum to the motor cortex through the disynaptic dentato-thalamo-cortical pathway [5]. Fibres from the dentate nucleus connect to the ventrolateral motor thalamus via the superior cerebellar peduncle. The motor thalamic cells project further to areas 4 and 6. The dentato-thalamo-cortical pathway itself is facilitatory. However, Purkinje cells of the cerebellar cortex inhibit the dentate nucleus. Therefore, activation of Purkinje cells results in disfacilitation of the motor cortex (cerebellar inhibition).

Physiological studies of cerebellar functions in humans are now becoming increasingly common, with the introduction of TES and transcranial magnetic stimulation (TMS) techniques allowing to investigate neural networks by stimulating neural structures in humans non-invasively. The motor evoked potential (MEP) to single pulse TMS of M1 is used to measure the motor cortical excitability. A conditioning stimulus over the cerebellum preceding a test stimulus over the contralateral M1 enables us to study the cerebellar regulatory effects on M1. In healthy subjects, cerebellar conditioning TMS inhibits the amplitude of the test MEP, when it precedes the test stimulus by 5 to 7 ms [6, 7]. This inhibition is mediated through the pathway between the cerebellum and M1 and has therefore been termed cerebellar brain inhibition (CBI). It is likely that cerebellar TMS activates Purkinje cells of the cerebellar cortex, leading to an increased inhibition of the disynaptic dentate-thalamo-cortical facilitatory connection, and then finally resulting in the observed inhibition of M1 [8–10].

Recently, it has been shown that CBI can effectively be modulated by tDCS, another non-invasive brain stimulation technique. The application of cathodal tDCS, which reduces cortical excitability, leads to a lasting inhibition of CBI for up to 30 min after stimulation. On the other hand, anodal tDCS, which increases cortical excitability, increases the magnitude of CBI, when applied over the cerebellum. This suggests that cerebellar tDCS leads to a sustained and polarity-dependent bidirectional modulation of cerebellar excitability by changing tonic Purkinje cell activity [11].

Cerebellar TMS finds application also as a diagnostic tool. The neurological examination alone does not allow the determination of the exact localization of a lesion in ataxic patients, since cerebellar ataxia may be caused by a lesion anywhere within the fronto-pontine-cerebello-thalamo-cortical loop. This loop consists of the cerebellar afferent pathways and the cerebellar efferent pathways including cerebellar output fibres (Fig. 1). Cerebellar TMS allows to assess the cerebellar efferent pathways and may therefore be useful to clinically differentiate cerebellar efferent ataxia from cerebellar afferent ataxia [9].

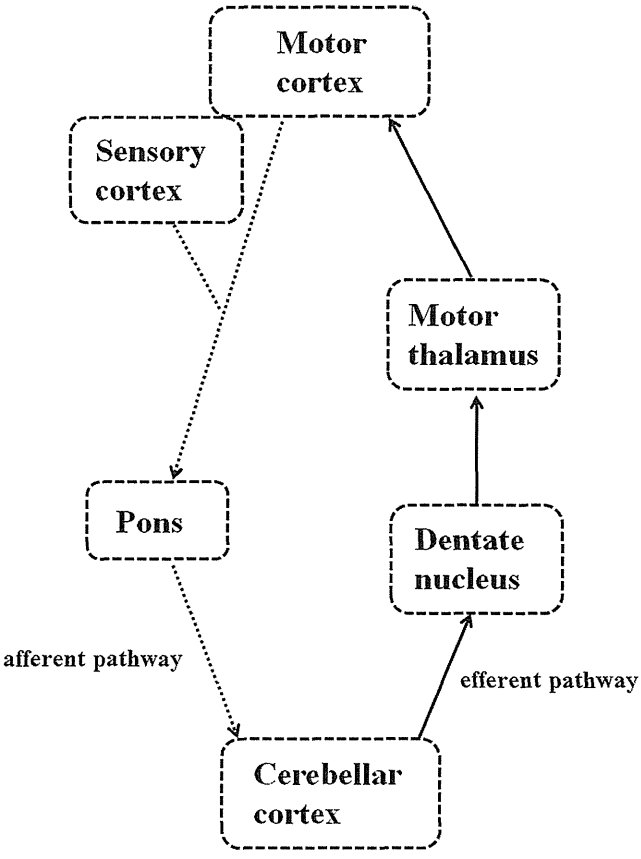

Fig. 1 Simplified scheme of the fronto-pontine-cerebello-thalamo-cortical loop. *Solid lines* indicate the cerebellar efferent pathways and *dotted lines* the cerebellar afferent pathways (from Groiss and Ugawa [10], with permission)

Patients with diseases affecting the cerebellar cortex, e.g. cerebellar cortical atrophy, spinocerebellar ataxia, multiple system atrophy (cerebellar type) or cerebellar stroke, showed impaired CBI [12, 13]. Involvement of the dentate nucleus, such as dentatorubral-pallidoluysian atrophy or Wilson's disease, also reduced CBI [12, 13]. In contrast, ataxic patients with involvement of cerebellar afferent pathways, such as pontine infarction, or involvement of the middle cerebellar peduncle had normal CBI. Moreover, patients without cerebellar involvement, e.g. Parkinson's disease, motor neuron disease or peripheral neuropathy, show normal CBI [12, 13].

Patients with progressive supranuclear palsy (PSP) had significantly reduced CBI without clinically detectable cerebellar signs [14]. This is consistent with pathological and radiological findings of PSP revealing an involvement of the cerebellar dentate nucleus and superior cerebellar peduncle. It indicates that cerebellar TMS revealed masked cerebellar dysfunction in PSP.

Ataxic hemiparesis is a lacunar syndrome with ataxia accompanying ipsilateral corticospinal tract impairment. In such patients, ataxia may result from a small lesion anywhere within the fronto-pontine-cerebello-thalamo-cortical loop. In

those patients, cerebellar TMS differentiated cerebellar efferent ataxia from cerebellar afferent ataxia. Their results are consistent with the well-known anatomical knowledge of the cerebellar circuits [15].

Besides these advantages, cerebellar TMS may present some limitation: suprathreshold cerebellar stimulation may induce antidromic pyramidal tract co-activation, which can affect cerebellar stimulation experiments [6, 16]. However, when the stimulation threshold is carefully defined using rectified electromyography and current direction and stimulation site are accurately and appropriately chosen [7, 17], cerebellar TMS has been proven to be a powerful and reliable method to investigate cerebellar function in humans non-invasively [16]. The localization and direction of cerebellar and brainstem stimulation are usually comparable and the intensity of cerebellar stimulation is defined relative to the threshold for descending motor tract activation at the brainstem level.

Taken together, these results suggest that cerebellar TMS is an effective and valuable method to evaluate the cerebello-thalamo-cortical loop function in humans and may be useful for pathophysiological analysis of ataxia.

Dynamic Modulation of Cerebellar Excitability

Dynamic modulation of cerebellar excitability by non-invasive stimulation is a relatively new concept. However, the development of such procedures is of significant interest to further the understanding of cerebellar functions and as a potential rehabilitation tool. There is no direct way in which cerebellar excitability can be assessed in humans, although invasive perioperative electrical stimulation of cerebellar lobules VI, VII and IX may generate movements [18]. Therefore, research in this field has relied on the inhibitory tone the cerebellar cortex exerts over the contralateral M1 via the thalamus [12, 13, 19]. Initial studies applied rTMS over the cerebellar cortex, producing a "virtual lesion" which is thought to decrease cerebellar output. This is valid for low-frequency rTMS, but rTMS might rather exert an exciting effect. The subsequent neurophysiological effects of this "virtual lesion" were then determined indirectly by testing M1 excitability with TMS. One would predict that this should result in an increase in M1 excitability, yet the findings were inconsistent. Some studies described an increase in intracortical M1 excitability [20, 21] but others a decrease [22, 23]. The reasons for these differences remain elusive; however, the application of different rTMS protocols and measures of M1 excitability among the various studies makes a direct comparison difficult.

Rather than measuring M1 excitability, assessing CBI [19, 24] allows one to probe the current excitability level of the cerebellum (see previous section). Galea et al. [11] applied anodal, cathodal or sham tDCS to the cerebellar cortex. Following 25 min of stimulation, it was found that cathodal tDCS resulted in a clear decrease of CBI suggesting reduced cerebellar excitability, whereas anodal increased it. Similar decreases in CBI have been found with inhibitory rTMS protocols [25]. However, unlike rTMS, the tDCS effects were specific to the cerebellum as no changes were observed in isolated measures of M1 excitability. These results suggest that tDCS and rTMS can modulate cerebellar excitability with the changes lasting up to 30 min after stimulation has ended [11, 25], but also indicate that there are subtle differences in how rTMS and tDCS may act on the cerebellum and its cortical connections.

Despite these dissimilarities, recent work has shown that rTMS and tDCS can lead to similar results of cerebellar modulation. Hamada et al. [26] and Popa et al. [27] used tDCS and rTMS, respectively, to induce changes in cerebellar excitability during M1 paired associative stimulation (PAS), a protocol to induce long-term potentiation-like plasticity in M1. Both studies found that protocols which are thought to increase cerebellar excitability lead to abolition of PAS-induced M1 plasticity. This demonstrates a key role of the cerebellum in priming M1 plasticity possibly through the processing of sensory information [26–28]. These results could have interesting clinical implications for dystonia patients, a disease where hyperplasticity in M1 leads to pathological co-contraction and abnormal postures [26].

At present, the clinical applications of non-invasively modulating cerebellar excitability have mainly been applied to Parkinson's disease patients who suffer from levodopa-induced dyskinesias, a symptom proposed to be, in part, due to over excitation between the cerebellum and cortex. Koch et al. [29] showed that a 2-week inhibitory rTMS protocol over the cerebellum leads to a reduction in these clinical symptoms. This was associated with decreased activity of the pathway that connects the cerebellar cortex with the deep cerebellar nuclei, measured with positron emission tomography imaging [29, 30]. Crucially, this provides evidence that non-invasive stimulation can produce plasticity changes in the cerebellum which are clinically relevant and that are observable weeks after stimulation has ended.

Although the aforementioned research highlights that rTMS and tDCS can dynamically modulate the excitability of the human cerebellum, there are many unresolved questions. First, animal studies are required to investigate how non-invasive stimulation modulates the cerebellum and in particular which neuronal populations in the cerebellum are receptive to such plasticity protocols. Second, with the emerging field of concurrent TMS/tDCS and functional magnetic resonance imaging (fMRI), it should be possible to study the neural consequences of non-invasive cerebellar modulation in order to gain better insights into the myriad of cerebellar functions. Although it is known that cerebellar stimulation

alters M1 excitability, the cerebellum has reciprocal connections with many other areas of the cortex and also with basal ganglia [31]. Therefore, it will be interesting in the future to investigate whether dynamic modulation of the cerebellum leads to activity changes in other connected areas of the brain.

tDCS of the Cerebellum: from Rodent Studies to Cerebellar Ataxias

The interest of tDCS as a research technique to promote neuroplasticity and as a therapeutic tool is growing [32, 33]. tDCS is now considered a potentially valuable clinical tool for neurorehabilitation interventions [34]. The extent of research applications is growing to emerging fields such as BCIs, widening considerably the future applications [35]. In the vast group of neurological disorders, cerebellar ataxias are amongst the most disabling [36]. Cerebellar ataxias are highly heterogeneous in terms of pathogenesis, region of the cerebellum affected and rates of progression. One subgroup gathers progressive degenerative disorders, which can have either a sporadic or a genetic origin. No cure exists for these degenerative forms of cerebellar ataxias [36].

Rodents are commonly used to assess novel therapeutic strategies and to identify mechanisms of action of therapies under development. In particular, there is a great need for novel animal models to test the effects of DCS in order to improve our understanding of complex cerebral processes [37]. Due to numerous similarities in terms of structure of the cerebellar circuits, neurostimulation studies in rodents might be helpful to extract principles applicable to human cerebellar ataxias.

Studies in rats confirm that DCS induces a polarity-dependent site-specific modulation of brain activity [38]. The cerebellum is known to receive numerous sensory inputs to participate in sensory processing and plays a critical role in the modulation of motor cortex excitability following peripheral sensory stimulation, allowing both the maintenance and the fine tuning of corticomotor discharges. Nevertheless, the exact mechanisms by which cerebellum interacts with motor cortex are a matter of debate. Acute cerebellar lesions cause a depression in the excitability of contralateral motor cortex [39, 40]. Enhanced inhibition within the motor cortex has been reported in several studies [41, 42]. Hypoexcitability of both the motor cortex and the anterior horn of the spinal cord are two major defects associated with acute cerebellar lesions, especially when the lesion involves lateral/interposed cerebellar nuclei or is extensive such as in hemicerebellar ablation. These changes are involved in the pathogenesis of the deficits of skilled movements in cerebellar patients. The analysis of the effects of anodal/cathodal DCS applied epidurally over the cerebellum, in rats, shows that anodal DCS of the cerebellum reduces the excitability of the motor cortex, as confirmed by the analysis of the recruitment curves of corticomotor responses and the analysis of the amplitudes of corticomotor responses [43]. Interestingly, it reshapes the representation of agonist/antagonist muscles in the motor cortex. Moreover, it decreases the excitability of the anterior horn of the spinal cord. Cathodal DCS of the cerebellum, on the other hand, exerts partially reversed effects as compared to anodal DCS in terms of modulation of the spatial representation of agonist/antagonist muscles in the motor cortex. Cathodal DCS of the cerebellum cannot be viewed as simply the reverse of anodal DCS. Results obtained with anodal DCS can be interpreted in terms of disfacilitation of the dentato-thalamo-cortical pathway: anodal DCS increases the inhibition exerted by Purkinje neurons over cerebellar nuclei, thus removing the facilitatory cerebellofugal drive exerted by cerebellar nuclei on extracerebellar structures such as thalamic nuclei [43].

One of the neurophysiological findings in cerebellar disorders associated with degeneration of the cerebellar cortex is the enhancement of long-latency stretch reflexes, as a consequence of a disinhibition of cerebellar nuclei [44]. Anodal cerebellar tDCS reduces the magnitude of long-latency responses in the upper limbs of patients who do not exhibit deficits of force [45], confirming that this form of DCS restores, at least partially, the inhibitory activity exerted by Purkinje neurons over cerebellar nuclei. The effects are not likely to be the consequence of a direct action on extracerebellar targets, such as a direct stimulation of brainstem nuclei. Indeed, the studies by Jayaram et al. [46] and Galea et al. [11, 47] have shown no effect of cerebellar DCS on the excitability of brainstem nuclei such as vestibular or trigeminal nuclei.

The tDCS-induced modulation of motor cortex discharges and cerebellar activity opens the road for tDCS applications in human cerebellar ataxias, including wearable applications during daily life since gait and posture are commonly impaired in cerebellar ataxias. tDCS applied over the cerebellum in humans modulates locomotor training in neurological patients with gait impairments [46] and speeds up learning of reaching [47, 48]. Cerebellar tDCS also finds application in the study of the cognitive cerebellar functions. Cerebellum is deeply involved in numerous aspects of behaviour. tDCS over the cerebellum tunes attention, verbal working memory, and might affect the processing of facial expressions [49–52].

Use of cerebellar stimulation to tune motor function is not a novel idea [53]. For instance, Cooper observed that cerebellar stimulation reduces the amplitudes of somatosensory evoked responses. Spasticity and epilepsy have been considered as disorders which could be improved by cerebellar stimulation [53]. Overall, the large group of neurological disorders in which a manipulation of cortical excitability might be beneficial—for instance to stimulate the plastic changes underlying learning and the process of recovery—are potential therapeutic targets for DCS [43]. Future studies are required to better define how DCS affects individual cerebellar symptoms,

given the topographical organization of cerebellar symptoms. One possible future direction in the emerging field of cerebellar neuromodulation is to combine DCS of the cerebellum with DCS of the extracerebellar structures critically involved in motor control such as motor/premotor cortex.

Paired Associative Stimulation of Human Cerebellum and Primary Motor Cortex

PAS is a now broadly used TMS protocol that allows induction of bidirectional spike-timing-dependent plasticity (STDP)-like changes in corticospinal excitability and/or effective connectivity of the stimulated pathway [54]. Depending on the interstimulus interval between an afferent input into the M1 and action potential generation in M1 corticospinal neurons by suprathreshold TMS, long-term depression (LTD)-like or long-term potentiation (LTP)-like plasticity of corticospinal neurons occurs. These effects are akin to STDP as studied in single cells in brain slices or neuronal cultures [55]. At the systems level of human M1, bidirectional STDP-like plasticity has been shown after repeated pairing of TMS of M1 with afferent input into M1 from peripheral nerves [56–58], ipsilateral ventral premotor cortex [59] and supplementary motor area [60].

In a recent study, we tested the possibility to induce STDP-like plasticity along the cerebellar-dentato-thalamo-M1 connection by cerebellum-to-M1 (CB→M1) PAS in healthy subjects [28]. Conditioning stimulation over the right lateral cerebellum preceded focal TMS of the left M1 hand area by 2 ms (CB→M1 PAS_{2ms}), 6 ms (CB→M1 PAS_{6ms}) or 10 ms (CB→M1 PAS_{10ms}) or randomly alternating intervals of 2 and 10 ms (CB→M1 $PAS_{Control}$). TMS of the left M1 was performed with a 70-mm figure-of-eight coil, TMS of the right lateral cerebellum with a 110-mm double-cone coil. MEP were recorded in the first dorsal interosseous muscle (FDI) of the right hand as readout for changes in corticospinal excitability. In addition, cerebellar–motor cortex inhibition (CBI; see section "Cerebellar Neurostimulation. What Have We Learnt from TMS Studies?") was measured as an index for effective connectivity of the stimulated cerebello-dentato-thalamo-cortical pathway according to an established protocol [9].

We found that CB→M1 PAS_{2ms} resulted in MEP potentiation, CB→M1 PAS_{6ms} and CB→M1 PAS_{10ms} in MEP depression, and CB→M1 $PAS_{Control}$ in no change (Fig. 2). The MEP changes lasted for 30–60 min after PAS. CBI decreased non-specifically after all PAS protocols.

Findings indicate that PAS of the cerebello-dentato-thalamo-M1 pathway can induce bidirectional long-term (>30 min) STDP-like plasticity of corticospinal excitability, extending previous studies that showed bidirectional STDP-like plasticity of corticospinal excitability when M1 stimulation was paired with associative stimulation of other input pathways [58–60].

The observed CB→M1 PAS-induced changes in MEP amplitude may be then explained as follows: rTMS of M1 at a time when lateral cerebellum conditioning stimulation has inhibited this tonically active pathway should lead to Hebbian LTD-like MEP decrease, similar to LTD induced in hippocampal slices when a high-frequency conditioning input was negatively correlated in time with a test input [61]. Given a CBI-onset latency of 5–6 ms [9], CB→M1 PAS intervals of ≥6 ms should lead to LTD-like plasticity and this is what was found (Fig. 2). The LTP-like MEP increase after CB→M1 PAS_{2ms} implies a reversal of the order of these events, i.e. action potential generation in M1 corticospinal cells regularly occurred at a time when the tonic excitatory dentato-thalamo-M1 input was active above average.

Our data are in agreement with two 1 Hz rTMS studies of the lateral cerebellum, which demonstrated an increase in MEP amplitude [20, 22]. Low-frequency rTMS leads to excitability depression of the stimulated brain area [62]. Therefore, the putative depression of Purkinje cell excitability would lead to reduced inhibitory regulation of the dentate-thalamo-M1 pathway and consequently to increased tonic excitatory input to M1.

Our experiments did not reveal a differential effect of CB→M1 PAS on CBI but rather a non-specific decrease independent of CB→M1 PAS interval. Other recent studies demonstrated a significant CBI increase after anodal versus a CBI decrease after cathodal transcranial direct current stimulation of the lateral cerebellum [11], and a CBI decrease after 1 Hz rTMS or continuous theta burst stimulation [63], without changes in MEP amplitude. While the reasons for these differences need further exploration, together these findings indicate that the modifications of corticospinal excitability (indexed by MEP amplitude) and CBI are often dissociated.

The bidirectional modification of M1 excitability induced by CB→M1 PAS may prove useful for correcting abnormal M1 excitability caused by cerebellar disease. Future studies may investigate the behavioural significance of this plasticity, in particular with respect to motor skill performance and motor adaptation.

The Cerebellum and Visually Guided Tracking Tasks

Visually guided tracking tasks are very commonly impaired in cerebellar ataxias, highlighting the importance of the cerebellum in the execution and regulation of these tasks which combine visual information and voluntary motor reactions. Recent works have shown that the cerebellum modulates muscles responses involved in this kind of activity. TMS over the cerebellum induces long-latency electromyographic (EMG) response in the soleus muscle in stance [64, 65]. Peak latency of this response is as long as 100 ms. Recently, another study found that cerebellar TMS induces long-latency fluctuation of

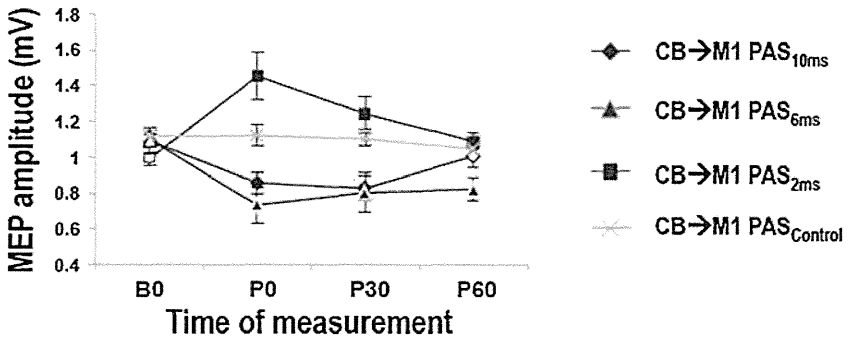

Fig. 2 Means (±SEM) of MEP amplitude (in millivolt) are depicted at baseline (B0), immediately (*P0*), 30 min (*P30*) and 60 min (*P60*) after CB→M1 PAS (*rhomboids*, CB→M1 PAS_{10ms}; *triangles*, CB→M1 PAS_{6ms}; *squares*, CB→M1 PAS_{2ms}; *crosses*, CB→M1 $PAS_{Control}$). *Filled symbols* denote significant differences in MEP amplitude after CB→M1 PAS compared to B0. Note significant MEP suppression at P0 and P30 after CB→M1 PAS_{10ms} and at P0–P60 after CB→M1 PAS_{6ms} but MEP potentiation at P0–P60 after CB→M1 PAS_{2ms}. In contrast, MEP amplitude remained unchanged after CB→M1 $PAS_{Control}$ (modified from Lu et al. [28])

index finger movement with an onset latency of 90 ms, and long-latency EMG response in the FDI muscle with an onset latency of 70 ms during a visually guided manual tracking task [66]. In order to evoke these responses, TMS was delivered 1 cm below and 3 cm right to the inion, at which the right cerebellar cortex is efficiently stimulated. Interestingly, the probability of the response induced by cerebellar TMS was higher than that induced by sham TMS during the visually guided manual tracking task, but this difference was absent when maintaining the finger at a stationary target. Accordingly, it has been assumed that this response may partially reflect task-dependent cerebellar activity.

A concern about these findings was that the long-latency finger fluctuation induced by cerebellar TMS may have been caused by motion artefacts in the neck. Thus, a subsequent study was conducted in order to rule out this possibility [67]. The probability of long-latency index finger fluctuation induced by cerebellar TMS was not significantly different from that induced by magnetic stimulation over the neck. Accordingly, a hypothesis that long-latency finger fluctuation induced by cerebellar TMS is partially due to the TMS-evoked neck twitch was not ruled out in this study.

Task dependency of long-latency EMG responses in the FDI muscle induced by cerebellar TMS was investigated in the same study [67]. It was expected that the long-latency EMG response would preferentially appear during the visually guided manual tracking task if the response reflects cerebellar activity because cerebellar activity is enhanced during visually guided task [68]. As expected, the probability of long-latency EMG responses induced by cerebellar TMS was significantly higher than that induced by TMS over the neck or than that induced by sham TMS during the continuous visually guided manual tracking task in which the subject tracked an oscillatory moving target, but these significant differences were not present during the other motor tasks; a discrete visually guided manual tracking task in which the subject tracked a target moving to one direction for a short period of time, a phasic movement task and a tonic contraction task. Accordingly, it was concluded that the long-latency EMG responses in the FDI muscle induced by cerebellar TMS are not due to neck twitch and preferentially appear during a continuous visually guided manual tracking task.

The latency of eye movements and the frequency of corrective saccades increase, and the correlation between eye and hand movement decreases, during visually guided manual tracking tasks in baboons with lesion of the dentate nucleus ipsilateral to the hand tested [69]. Accordingly, long-latency EMG responses, which preferentially appear during continuous visually guided manual task, may be a useful probe for investigating particular cerebellar activity during a visually guided manual tracking task.

What are the pathways mediating long-latency EMG responses induced by cerebellar TMS? The pathways mediating this response may partially share common pathways with those controlling visually guided manual tracking tasks because this response preferentially appears during visually guided manual tracking. The pathways mediating long-latency EMG response in the FDI muscle must be polysynaptic because of its long latency. Because the long-latency EMG response is a motor response, this response partially reflects activity of the efferent motor pathways. However, it is also apparent that this response does not reflect direct stimulation of the spinal cord because of the different latencies. On the other hand, the long-latency EMG response is not likely to be mediated by dentate-thalamo-cortical pathway, as CBI might suggest [7, 8, 70] (see section "cerebellar inhibition") because the response appears with an onset latency of 70 ms [66, 67]. A previous study using optokinetic stimulation suggests that the vestibulospinal tract mediates long-latency EMG response induced by cerebellar TMS in the soleus muscle in stance [65]. In spite of that, it is not certain that long-latency EMG response in the FDI muscle is mediated by this pathway. In order to identify the pathways mediating long-latency EMG response induced by cerebellar TMS, further investigations are needed.

The Cerebellum and Motor Surround Inhibition

Surround (or lateral) inhibition is a term usually used to describe a key property of the sensory system in which activation of a central receptive field causes direct inhibition of the surroundings [71–75]. Within the motor system, it was first explored conceptually as a mechanism by which basal ganglia circuits might selectively execute desired motor programs [71]. Later, a potential neurophysiological measure of motor surround inhibition (mSI) was demonstrated; by stimulating the motor cortex using TMS at the onset of movement of the index finger, suppression in the size of responses of non-synergistic surround muscles was seen [72] (Fig. 3a). The potential clinical importance of mSI is supported by several electrophysiological studies in dystonic patients, which reveal that the involuntary co-contraction of hand muscles that occurs in this condition is associated with a disruption of mSI [75].

It is not known which structures within the central nervous system are important for the generation of mSI. Some authors favour a neocortical mechanism, mainly because mSI has only been demonstrated after cortical stimulation. Electrophysiological studies [72, 75] of spinal excitability (H-reflex, F wave) at the onset of a voluntary movement failed to show topographic-specific modulation of excitability at the spinal level. Further studies on the dependency of mSI on intrinsic primary motor cortical inhibitory networks (SICI, LICI, cSP) or premotor–motor cortex interactions have failed to associate specific neuronal networks with the generation of mSI [72, 75–77].

Some characteristics of cerebellar function make it a suitable candidate to contribute to the generation of mSI. Most obvious is the cerebellum's role in the coordination of movement. Deficiencies in hand control and timing of individual finger movements are seen in patients with cerebellar disease [78]. Furthermore, it has been shown that the cerebellum has a net inhibitory effect on the cerebral cortex via the cerebello-dentato-thalamo-cortical pathway, an inhibitory pathway that could potentially mediate mSI [7, 79]. Despite this net inhibitory effect exerted by the cerebellar cortex, cerebellar nuclei still exert overall an excitatory action on their targets.

Two electrophysiological studies have explored the role of the cerebellum in the generation of mSI. These studies explored CBI in active and surround muscles of the hand at movement onset when mSI is most prominent [72, 75]. CBI was found to be reduced in both active and surround muscles at the onset of movement. However, muscle-specific modulation of CBI at onset of movement in parallel with mSI was not confirmed and thus the study did not provide evidence of a functional link between CBI and mSI (Fig. 3b) [73].

CBI relies on a powerful (and fairly painful) phasic topographically—relatively as compared to tDCS—specific magnetic stimulation of the cerebellum that might not reveal subtle cerebellar contributions to mSI. A further study therefore explored the effect of cerebellar tDCS on mSI [74]. In the study of Galea et al., the cerebellum is stimulated applying a cathodal stimulation for 15 min, and changes in excitability are seen up to 30 min after the stimulation [11]. The effect of this stimulation has been confirmed neurophysiologically (measuring CBI) and behaviourally (measuring rates of adaptation to sensory perturbations, a cerebellar-dependent learning task) [11, 47]. mSI was tested before and after both anodal

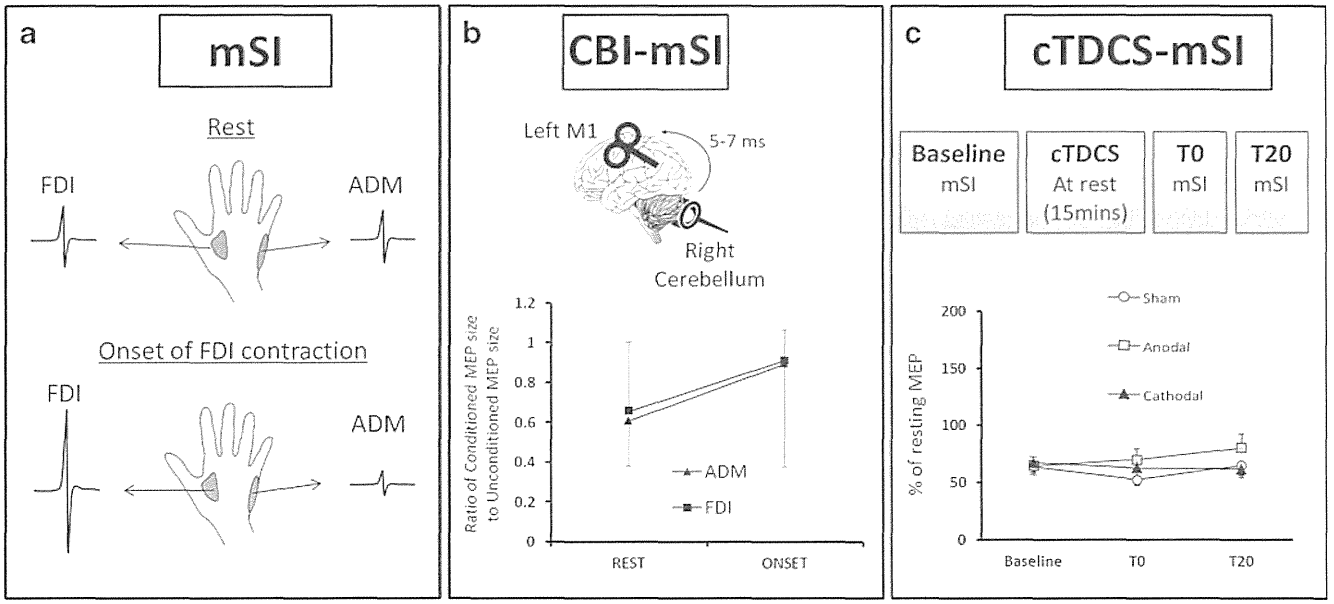

Fig. 3 **a** mSI in the surround ADM muscle at the onset of an index finger flexion (FDI synergist). **b** Non-topographic-specific modulation of CBI at the onset of finger flexion (FDI synergist muscle, ADM surround muscle). **c** Non-significant change in mSI in ADM muscle 0 min (*T0*) and 20 min (*T20*) after cerebellar TDCS (intensity 2 mAmps, duration 15 min) (modified from Kassavetis et al. [73] and Sadnicka et al. [74])

and cathodal cerebellar tDCS to investigate if the magnitude of mSI was modulated. Here, the hypothesis was that anodal tDCS would enhance mSI and cathodal tDCS would impair mSI. However, this study found no evidence that modulating the excitability of the cerebellum changed the magnitude of mSI (Fig. 3c).

In the computational motor control literature, the cerebellum is commonly considered to play a role in integrating predictions of the sensory consequences of movement with sensory feedback using an internal model of movement dynamics [80]. This process is essential for adaptation of future motor commands when sensory prediction errors are generated. The hypothesis that mSI is also capable of adaptation in response to sensory prediction error was explored in a study where vibration was used to generate sensory prediction error in a surround muscle [81]. Repetition of the movement with altered sensory feedback in a surrounding muscle lead to increases in the strength of mSI confirming that mSI is indeed subject to adaptation. In addition, this study suggested that motor commands are not spatially limited to active muscles and that mSI may represent an electrophysiological correlate of the part of motor command responsible for controlling the non-active surround muscles. It remains an open question whether cerebellar stimulation applied during the training session may affect the adaptation process shown in this study.

Thus, the role of the cerebellum in the generation and regulation of mSI is currently uncertain. There does not seem to be a direct relationship between CBI and mSI. Nor does modifying the activity of the cerebellum by tDCS change any characteristics of mSI. It may be that mSI is a fundamental inhibitory mechanism within the nervous system, and subtle alteration of the activity of one of the nodes within the mSI network does not allow a meaningful change in mSI to be observed. Alternatively, the genesis of mSI may reside within other areas such as the basal ganglia nuclei or local networks within the motor cortex itself. The adaptation of mSI in response to sensory feedback does suggest that the cerebellum may have a regulatory role over adaptation of mSI. Studies investigating the underlying physiology of mSI and the disruption of mSI in disease states are ongoing and are likely to provide further information on this topic in the future.

Cerebellar tDCS and Motor Learning

One of the fundamental abilities of the central nervous system is to learn new motor behaviours. This ubiquitous capacity has been extensively investigated in humans and animals. Motor learning, broadly defined as the ability to acquire a new motor behaviour that can be stored and expressed at a later time, involves different forms of learning with likely different neuronal mechanisms. One type is motor adaptation, typically defined as a short-term form of learning (minutes to hours) that is driven by sensory prediction errors [82, 83]. This form of learning is commonly used to return baseline levels of performance in the presence of a perturbation, for example, when manipulating an object with unknown or suddenly different characteristics (such as when learning to appropriately use a new tool or computer mouse). Another form is success-based learning, a slower process that is reinforced by successful goal completion [84, 85]. For example, when learning a novel motor skill where new muscle activation patterns lead to new abilities (i.e. learning a new sport, playing a musical instrument or a videogame).

The cerebellum has been recognized as a crucial structure involved in motor learning, in particular in relation to motor adaptation forms of learning [86]. This knowledge comes from testing patients with cerebellar damage who typically experience a reduced capacity to adapt to novel environmental demands [87–89]. Similarly, neurophysiological studies in animals have indicated that motor adaptation may be mediated by LTD processes in cerebellar Purkinje cells [90, 91]. Until recently, motor adaptation processes have been mostly investigated using imaging techniques and/or employing patients with cerebellar damage. However, more recent developments in non-invasive brain stimulation techniques have permitted studying the role of the cerebellum in motor adaptation.

Taking advantage of the CBI measure and of the possibity to indirectly infer the level of excitability of the cerebellum if M1 excitability is not changing or if these changes are accounted for [11], our recent series of experiments has assessed the role of the cerebellum in different forms of motor adaptation. One study has investigated the potential physiological substrates underlying locomotor adaptation. This type of motor adaptation has been extensively studied using a split-belt paradigm [92]. Here, participants' gait is assessed before, during and after being exposed to walking on a treadmill where one belt (and therefore one leg) moves two to three times faster than the other belt. When this happens, people experience a gait asymmetry or a limp. However, this can be corrected for within 10 to 15 min of walking at different belt speeds. In this paradigm, it is evident that the individual learns to correct for the perturbation because sudden removal of the perturbation elicits a behavioural after-effect characterized by a limp in the opposite direction. Using this task, we showed that the magnitude of CBI is reduced proportionally to the amount of locomotor adaptation. This correlation was present using two independent measures of learning and these effects were absent in control groups where learning did not occur. Importantly, M1 excitability did not change in association to this form of locomotor adaptation [92]. A second study investigating adaptation to a visual perturbation during reaching movements found similar results. Here, subjects performed fast reaching movements to move a computer screen cursor to different targets. After a baseline period, an unexpected 30° visual rotation (perturbation) was applied to the cursor causing

errors that could be adapted for by adjusting the reaching movements. Using this paradigm, we found that CBI, but not M1 excitability, is reduced early on when subjects are correcting for the visual perturbation, followed by a return to baseline CBI levels once the perturbation is accounted for. Importantly, changes in CBI were not driven by the mere presence of errors that could not be corrected (i.e. random perturbations), suggesting that the cerebellum is crucially engaged during the successful reduction of large errors [93].

Altogether, these studies indicated that CB-M1 connectivity changes are cerebellar dependent, rather than originating from M1, and are specifically linked to motor adaptation. Interestingly, the direction of CBI changes associated with learning seems consistent with the concept of LTD formation in cerebellar Purkinje cells [92, 93].

The crucial role of the cerebellum in motor learning processes has been corroborated in another line of studies using tDCS, known to modulate the excitability of the cerebellum [11]. Applying anodal tDCS (the excitatory form of stimulation) over the cerebellum during visuomotor reaching [47, 94] or locomotor adaptation [92] sped up the adaptation process resulting in faster error reduction. Importantly, when the inhibitory form of tDCS (cathodal) was applied over the cerebellum, the locomotor adaptation rate was reduced, indicating a polarity-specific effect of tDCS on the cerebellum [92].

In sum, it is possible to assess neurophysiological changes occurring in the cerebellum during adaptive motor learning and possibly other motor behaviours. Interestingly, this first series of studies emphasize the role of the cerebellum during motor adaptation and indicate specific connectivity changes that can be targeted to augment behavioural processes. Indeed, applying tDCS to increase cerebellar excitability resulted in faster adaptation in reaching and locomotor tasks. These findings suggest that cerebellar stimulation has the potential to become a useful neurorehabilitation strategy to improve motor function in patients with neurological conditions.

Cerebellar tDCS and Learning

Thanks to research over the past years the cerebellar involvement in learning can be "observed" during several tasks [95–97]. Cerebellar tDCS is a further fascinating development which allows researchers to manipulate functions in the human cerebellum and is a novel approach to study learning [98]. Preliminary modelling studies showed that the electric field generated during cerebellar DCS [48] effectively reaches the cerebellum (Fig. 4).

The first demonstration that cerebellar DCS could effectively influence cerebellar function came from a study from our laboratory describing its effects on proficiency in a working memory task in a group of healthy subjects [49]. Our experiments showed that cerebellar DCS blocked the practice-dependent increase in task proficiency. Evidence that tDCS over the dorsolateral prefrontal cortex increased task proficiency showed that the effect was specific, and given that cerebellar DCS, left visual evoked potentials unchanged ruled out possible non-specific effects arising from visual cortex stimulation. Hence, cerebellar DCS somehow inhibited the *learning of learning*. This observation opened the way to experiments exploring how cerebellar stimulation and the cerebellum itself influence several other types of learning.

Extending cerebellar learning research, Jayaram et al. [46] conducted experiments on motor learning. They found that anodal cerebellar tDCS applied during walking improved locomotor adaptation, whereas cathodal tDCS worsened it, without affecting the rate of de-adaptation to the new locomotor pattern. The results suggested that cerebellar tDCS could be used as a tool to modulate *locomotor learning* and training in patients with neurological disorders with gait impairments.

In a series of experiments conducted in healthy subjects, Galea et al. [47] found that cerebellar tDCS enhanced the acquisition process during adaptive motor learning, further supporting the idea that cerebellar modulation by DCS affects visuomotor learning and demonstrated that the cerebellum and primary motor cortex have distinct functional roles in the processes of acquisition and retention during adaptive *motor learning*.

A final major advance comes from further experiments conducted in our laboratory concerning cerebellar DCS-induced changes in human *procedural learning*, i.e. learning involving a set of automatic, non-conscious and unintentional processes important in structuring skills, perceptions and behaviour [48]. We designed these experiments to investigate whether cerebellar tDCS influences procedural learning as measured by the serial reaction time task (SRTT) and hence whether this structure intervenes directly in procedural learning. Healthy young participants performed the SRTT, a mood and fatigue visual analogue scale (VAS) and a visual attention task, before and after receiving anodal and sham cerebellar tDCS. The main finding in this study is that anodal cerebellar tDCS improved procedural learning as indexed by the SRTT in healthy subjects. Because scores in mood and fatigue VAS and visual attention task remained unchanged, the cerebellar tDCS-induced changes in SRTT performance did not reflect changes in arousal or alertness. Hence, the learning benefits provided by anodal cerebellar DCS may have promising implications for designing motor learning protocols in patients with cerebellar disorders undergoing neurorehabilitation and, possibly, for developing novel treatment strategies for deficits in procedural learning in conditions such as dyslexia and schizophrenia. rTMS of the cerebellum interferes also with procedural learning and impacts also on associative learning [99, 100]. In subjects who receive continuous theta burst stimulation (cTBS), conditioned responses in eyeblink classical conditioning tasks are fewer and their onsets are earlier [100].

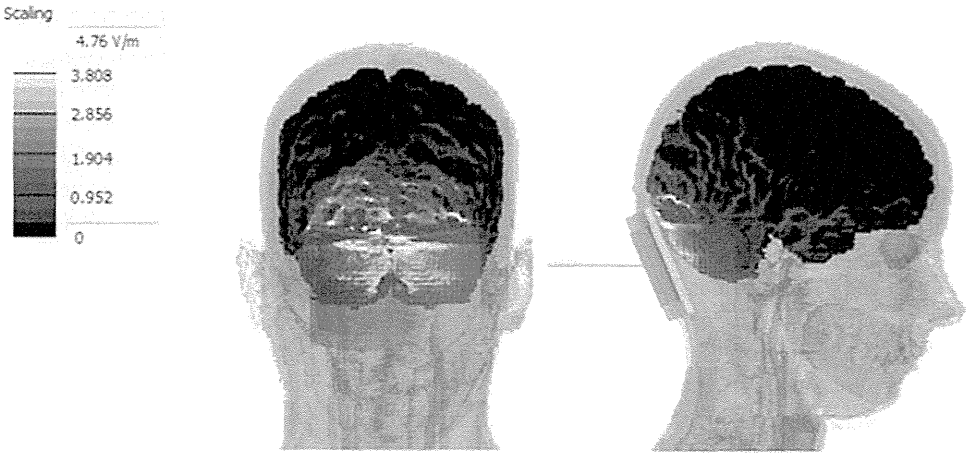

Fig. 4 This preliminary modelling study shows that the active electrode over the cerebellum with an extra-cephalic reference generates the maximum electric field density in the cerebellum. Back and lateral views of the E field distributions on the cortex and cerebellum with the reference colour scale for intensity (modified from Ferrucci et al. [48], with permission)

In conclusion, even though several important issues remain unresolved (i.e. the electric field geometry, the optimal stimulating electrode positioning, lack of polarity specificity in some behavioural tasks but not in others, the duration of the after effects and off-line/on-line stimulation) and studies on larger sample sizes are needed, available data suggest that cerebellar tDCS can be a valuable tool to manipulate the cerebellar "cockpit" for the various learning processes.

Cerebellar tDCS and Verbal Working Memory

Non-motor functions of the cerebellum have intensively been studied in the context of verbal working memory (VWM), the ability to maintain and manipulate (verbal) information that has just been experienced, but no longer exists in the external environment [101]. This essential cognitive faculty has been linked to a network of cerebral brain regions including prefrontal, parietal and temporal cortices [101]. Converging evidence from numerous neuroimaging, clinical and brain stimulation studies however suggests that not only cerebral regions but also the cerebellum contributes to VWM [1, 102].

VWM has been conceptualized as a multi-component system, consisting of a phonological store, which holds verbal information for a short delay, and an articulatory control process, which allows for refreshing information maintained within the phonological store by sub-vocal rehearsal [103]. Brain activity related to these VWM components has systematically been studied using item recognition paradigms such as the Sternberg task [104]. During the Sternberg task, participants see or hear a sequence of letters or digits ("encoding phase") which they have to maintain during a delay period ("maintenance phase"). Afterwards, they are asked to decide if a probe item matches one of the previously presented items ("retrieval phase"). Neuroimaging studies show that the superior cerebellum, including lobule VI and Crus I, is activated during the encoding of newly presented items and co-activates with lateral prefrontal regions involved in speech processing. It has therefore been suggested that the superior cerebellum is involved in generating an articulatory trajectory required to initiate articulatory rehearsal [105, 106]. In contrast, the right inferior posterior cerebellar lobules VIIb and VIII show task-related activity when items are maintained in mind over a delay and co-activate with inferior parietal regions implicated in storage-related processing. These findings led to the assumption that the inferior cerebellum contributes to phonological storage [105, 106].

Although neuroimaging studies clearly identified cerebellar activation during different VWM phases, these activations do not necessarily relate to cognitive processes but may also reflect task-related motor demands. Clinical studies in patients with cerebellar lesions, however, support the view that the cerebellum contributes to the cognitive demands of VWM [107]. A standard clinical test to capture VWM capacity is the Wechsler Memory Scale forward and backward digit span test [108]. During this test, sequences of digits of increasing lengths are presented at a rate of one item per second, and participants are asked to recall the sequences in forward or backward order. Patients with focal cerebellar lesions, due to stroke or tumor resection, presented shorter forward and backward digit spans, clearly confirming a cerebellar role in the cognitive processes involved [102, 109]. These deficits are most evident in patients with lesions involving the posterior lobe of the cerebellum [102], which agrees with neuroimaging data [1] and known anatomical connections between the posterior cerebellum and prefrontal cortical regions involved in higher order cognitive function [110].

As compared to patient studies, non-invasive stimulation offers the opportunity to study the cerebellar involvement in cognitive processes in healthy subjects without confounding factors such as pharmacological treatment, concomitant damage to other cerebral brain regions or compensatory plastic processes in cerebral regions due to cerebellar damage. A recent study applied tDCS over the right cerebellum in healthy

subjects to investigate its effects on digit spans [50]. Confirming a cerebellar role in VWM, the authors found shorter forward digit spans after cathodal stimulation [50], which is known to decrease neuronal excitability in the motor cortex and cerebellar–M1 connectivity [11].

Another study administered single-pulses TMS over the right superior cerebellum during the encoding phase of the Sternberg task [111]. Due to TMS pulses, reaction times during memory retrieval substantially increased confirming the causal role of the right superior cerebellum in VWM.

A role of the cerebellum even in cognitive practicing was suggested by a study investigating the influence of cerebellar tDCS on the practice-dependent increase in proficiency in the Sternberg task [49]. The authors found that cathodal as well as anodal cerebellar tDCS impair the known practice-dependent increase in reaction times in this task. This finding is in line with recent models of cerebellar involvement in higher order cognitive functions, which assume that the cerebellum automatizes cognitive processes originally taking place in other cerebral regions [112].

While the brain stimulation studies cited above found impairing effects of tDCS and TMS over the cerebellum on VWM, a recent tDCS study indicates that cerebellar stimulation can also enhance working memory performance [51]. In this study, participants were aurally presented with sequences of numbers and had to subtract a number heard from the number immediately before it. The authors found improved performance after cathodal tDCS as compared to anodal or sham tDCS. The crucial difference between Pope and Miall's task and the digit span task as well as the Sternberg task is the higher degree of executive processing involved, suggesting that the effects of cerebellar stimulation differentially interact with different levels of executive demand. Future studies will have to prove whether the direction of tDCS effects is a matter of the degree of executive demand.

In sum, recent non-invasive brain stimulation techniques confirmed the theory of a role of cerebellum in cognitive operations and proved a causal role of the cerebellum in different sub-processes of this essential cognitive faculty.

Cerebellar tDCS and Semantic Associations

Cerebellum is involved in associative processing. Very likely cerebellum applies its algorithms in a uniform fashion to its inputs, as pointed out in the "Introduction" [112]. These algorithms are well established to instantiate state estimation and feedforward control, fundamental for acquiring associations between and generating predictions about temporally contiguous events in sensory, motor, emotional and cognitive domains [113]. However, cerebellar contributions to semantic associations remain under-researched, while methodological issues with patient and imaging studies compromise the replication and interpretation of the few yet promising findings. Neurostimulation offers the potential of conducting methodologically robust experimentation capable of establishing direct cerebellar contributions to semantic associations.

The terms "semantic" and "associative" are vaguely used in the literature to denote different cognitive processes. Semantic associations are not restricted to the linguistic domain or to inter-lexical relations. Lexical priming studies help to distinguish semantic associations from semantic categorical relations and phrasal associations: *semantic associations* reflect the association of concepts based on world knowledge, as in "instrument–action" pairs ("broom–sweep"), "script relations" ("theatre–play"), "locative relations" ("beach–house") and "compositional relations" ("brick–house"). By contrast, *semantic categorical relations* rely on similarities and taxonomic relationships between units, as in paradigmatic co-exemplars within a category ("pig–horse"), or in subordinate–superordinate pairs ("storm–weather"). Finally, *phrasal associations* rely on the temporal contiguity of the particular units in processing, reflecting use rather than meaning, as in idioms ("gift–horse", "skeletons–closet") [114].

The emergent picture suggests that the cerebellum contributes to processing semantic and possibly phrasal associations, but not semantic categorical relations. The patient examined by Fiez and colleagues generated inappropriate, yet categorically related responses in word generation tasks (e.g. either "small", "take" or "swallow", in response to "pill"). This could not be attributed to overall cognitive impairment, as their performance on tests of memory, intelligence, "frontal function" and language skills was excellent, suggesting that cerebellar damage leaves semantic networks intact [115]. In another study [116], patients performed poorly in generating verbs for nouns, but selected the correct verb for a noun from a list of alternative responses, suggesting that semantic/syntactic representations were preserved. They also produced appropriate subordinate term responses to superordinate terms, suggesting that "[t]he right posterolateral cerebellum may be more involved in associative semantics than in categorical semantics" [116]. Non-motor-related cerebellar activations for verb-to-noun generation have also been shown in PET [117] and fMRI studies [118].

In a recent TMS study [119], noun primes preceding verb targets that could be categorically (e.g. "theft"–"stealing") or associatively related (e.g. "chef"–"cooking") were used in a lexical decision task. Stimulation of a lateral cerebellar site selectively boosted associative priming, while no effects were found after medial cerebellar stimulation or no stimulation at all. Moreover, neocerebellar TMS has been shown to also affect phrasal associative but not semantic categorical priming [120], as well as the acceleration of lexical decisions performed on previously encountered pairs of letter strings [121]. These findings are in line with patient [122] and TMS [123] studies showing that cerebellar lesions impair verbal

fluency by affecting phonemic rule-based word production, yet sparing semantic categorical rule-based performance.

Finally, evidence supports cerebellar involvement in semantic associations at the sentential level: In a TMS study, right lateral cerebellar stimulation selectively delayed participants' eye fixations to target objects predicted by the content of the sentences they were aurally presented with, while no effect was seen on fixations in sentences without predictable content [124]. Moreover, in a study employing a card-sequencing task, patients with left lesions performed poorly, selectively on script sequences based on pictorial material, while patients with right lesions only on script sequences requiring verbal elaboration [125].

The majority of evidence for cerebellar involvement in semantic associations comes from fMRI and patient studies. Methodological difficulties make the replication and interpretation of these findings problematic: cerebellar activation may be owed to sensorimotor and not cognitive task aspects. For instance, the lateral cerebellar activations yielded by Frings and colleagues were also found as a measure of noun reading in inner speech [118]. Similarly, the restricted subject pool of selective non-extra-cerebellar lesions, along with the great heterogeneity of the larger non-restrictive ones, makes the replication of findings such as verb generation impairments problematic [126].

Neurostimulation offers outstanding methodological advantages, allowing for larger subject pools and within-subjects repetition. It is conducted acutely, since time is insufficient for functional reorganization. Moreover, its sensorimotor effects are far from compromising the ability of subjects to participate in behavioural tasks or from inducing global cognitive impairments [127]. Above all, systematically comparing the effects of stimulation on cerebellar lobules and their cerebral cortical targets would offer the possibility to assess in a causal fashion whether cerebellar contributions to semantic associations are direct or modulatory.

The Cerebellum and Language. rTMS and Predictive Language Processing

Over the last decades, a considerable body of evidence has implicated the cerebellum in language processing. This evidence includes neuropsychological data from cerebellar patients, anatomical and functional evidence for connectivity between cortical language areas and the cerebellum, neuroimaging studies in healthy participants, and crossover evidence from dyslexia studies [128]. As stated in the "Introduction", the cytoarchitectonic homogeneity of the cerebellar cortex suggests a uniform computation [129]. Hence, it seems sensible to test the hypothesis that, in analogy to its predictive role in motor control [130], the cerebellum's contribution to linguistic function would also be characterised by short-term prediction and feedforward control.

Cerebellar patients may present with problems with lexical access and syntax, and with speech production deficits [128]. These deficits are interpreted as a failure of a cortico-cerebellar system comprised of frontal language areas and the lateral cerebellum. Indeed, posterolateral cerebellar areas are reciprocally connected to prefrontal cognitive areas [2]. Evidence from resting state functional connectivity studies demonstrates connections between the lateral cerebellum and frontal, parietal and temporal language regions [131]. Moreover, patients with right cerebellar lesions show selective hypoperfusion in Broca's area [129] and a recent fMRI study reported strong bidirectional effective connectivity between the right cerebellum and both left inferior frontal gyrus and left middle temporal gyrus [132]. Dyslexia has been linked to cerebellar deficits, and structural volumetric differences between dyslexics and controls have been found in the right cerebellum [133]. Right cerebellar activity is often found in functional imaging of language tasks [1, 134], and language localiser tasks can identify activity in the right cerebellum on an individual participant basis [135]. Thus, there is good reason to expect that TMS-induced disruption of right cerebellar cortex will affect language, and that this disruption may be specific to feedforward prediction processes.

However, to date, there have been few studies of the impact on language processing of TMS targeted at the cerebellum, although there are studies on related cognitive aspects such as verbal working memory [111].

Argyropoulos [120] was the first to use TMS to depress cerebellar activity in a linguistic task. By applying cTBS to the medial and lateral cerebellum in a lexical priming task, he reported a selective drop in accuracy of lexical decisions for medial stimulation, which was seen only in the first of two repeated stimulation sessions that were separated by 3–26 days. The medial site and the temporary effect of the manipulation leave some open questions about whether this was a genuine impairment of lexical priming. Argyropoulos also reports that there is some overlap with oculomotor areas that might confound his results, although it could be argued that this might apply to all tasks and therefore not account for a result specific to lexical decisions. However, in 2012, Argyropoulos and Muggleton [119] used cTBS over lateral cerebellum and reported a four-way interaction effect of selective enhancement of semantic associative noun-to-verb priming post-stimulation. This enhancement might reflect neocortical disinhibition [19, 51], but it is also possible that their effect was in fact a reduction of the practice-induced improvement in response times in one condition, as such improvement was seen in other groups including no-stimulation controls. Arasanz et al. [123] have also used cTBS and reported reduced category switching (reduced phonemic and semantic fluency) after right cerebellar stimulation/depression.

Finally, Lesage et al. [124] applied rTMS over the right cerebellar hemisphere (directed towards Crus II) in a linguistic

prediction task and monitored the latency of eye movements made towards pictures of target items referred to in spoken sentences. In the baseline, before application of rTMS, there was a 350-ms advantage in saccadic response times (Fig. 5), if the verb predicted a single target object later in the sentence (as in "The man will sail the ... boat/mountain/bird/car"), compared to non-selective verbs ("The man will watch the ... boat/mountain/bird/car"). Following 10 min of 1 Hz rTMS, this advantage was reduced by 100 ms. Importantly, there was no change in saccadic latencies in the non-predictive sentences, ruling out a general effect on language processing. There was also no change in eye movement kinematics, ruling out latency effects due to impaired oculomotor control. This evidence suggests that the predictive role previously ascribed to the cerebellum, based on motor studies [130], can be extrapolated to language, although whether the contributions of the cerebellum in these functions are strictly identical remains to be seen.

Conclusion: Points of Consensus and Issues Requiring Further Research

The field of neurostimulation of the cerebellum with TMS and tDCS is gaining in popularity in the scientific community. There is a consensus amongst the panel of experts that both techniques influence effectively cerebellar functions in the motor and non-motor domain. The experts agree that similarities have been discovered from the diverse areas of research. There are converging evidence that both TMS and tDCS modulate the activity of the neuronal circuits between the cerebellum and the primary motor cortex, exerting a tuning effect on cerebellar excitability and impacting on the motor and cognitive contributions of the cerebellum. As highlighted in the "Introduction", cerebellum may have a similar role across multiple functions. Results of cerebellar neurostimulation studies reinforce this concept. There is a general agreement that cerebellar TMS is a valuable method to study the cerebello-thalamo-cortical loop functions, and that DCS induces a polarity-dependent site-specific modulation of cerebellar activity. However, several important technical issues remain unsolved, such as the exact positioning of electrode stimulation or the duration of the after effects for tDCS. Further studies should be performed to address these issues. Moreover, the experts agree that the role of TMS to enhance cerebellar plasticity is still not established. The demonstration is lacking both in animal studies and in human experiments aiming to promote cerebellar plasticity either at a cellular level, at a system level or in terms of cerebello-cerebral or even cerebello–brainstem–spinal networks. Future investigations should also attempt to establish how DCS affects individual cerebellar symptoms in cerebellar ataxias, given the topographical organization of cerebellar deficits. Furthermore, the long-term consequences of cerebellar neurostimulation remain to be defined. Further research with long follow-up periods should be performed since non-invasive neurostimulation of the cerebellum is a growing field. Indeed, besides the huge potential in terms of physiological studies of the cerebellar, the clinical applications in cerebellar disorders are likely numerous. Rigorous clinical trials should be encouraged to clarify whether

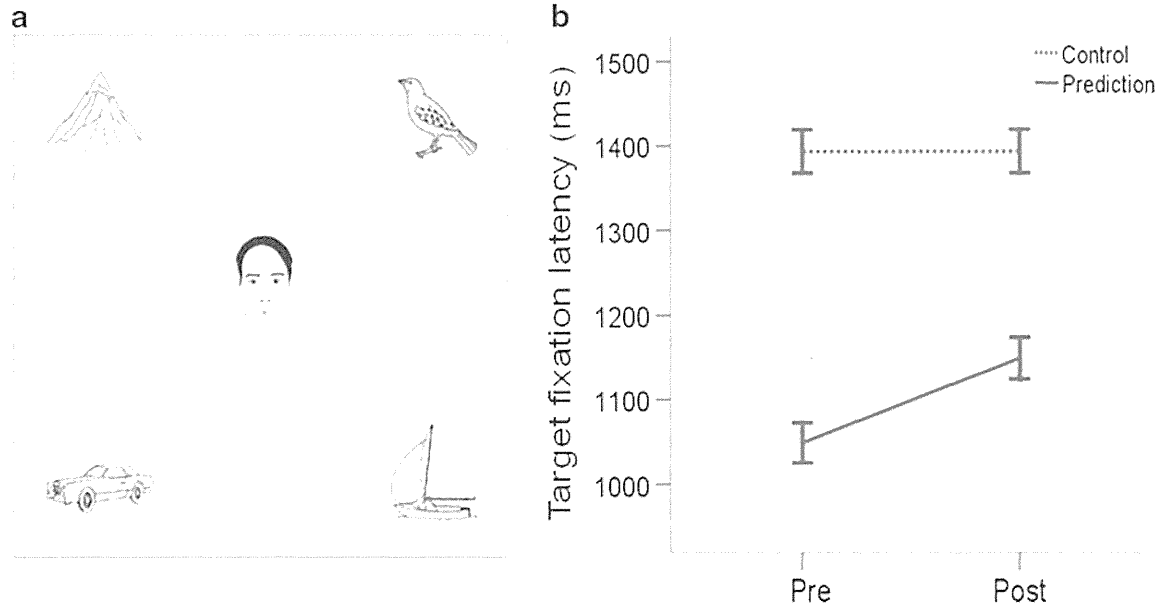

Fig. 5 **a** Example of a scene in the Visual World paradigm. In the prediction condition the direct object of the sentence can be predicted from the verb whereas in the control condition such prediction is not possible. **b** Target fixation latencies before and after rTMS to the right lateral cerebellum. rTMS significantly reduced the advantage for the prediction condition (*solid line*), while fixation latency in the control condition (*dashed line*) was unaffected (modified from Lesage et al. [124], with permission)

these techniques might have a therapeutic role in cerebellar disorders and how they might be included in the list of validated therapies.

Conflict of Interest We have no conflict of interest to declare.

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ORIGINAL PAPER

Visual Scanning Area is Abnormally Enlarged in Hereditary Pure Cerebellar Ataxia

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Abstract The aim of paper was to investigate abnormalities in visual scanning using an eye-tracking device with patients with spinocerebellar ataxia type 6 (SCA6) and SCA31, pure cerebellar types of spinocerebellar degeneration. Nineteen SCA patients (12 patients with SCA6 and 7 patients with SCA31) and 19 normal subjects in total participated in the study. While the subjects viewed images of varying complexity for later recall, we compared the visual scanning parameters between SCA patients and normal subjects. SCA patients had lower image recall scores. The scanned area in SCA patients was consistently larger than that in normal subjects. The amplitude of saccades was slightly larger in SCA patients than that in normal subjects, although it did not statistically differ between the two groups and correlated significantly with the scanned area in most images in SCA patients. The instability ratio of fixation, reflecting gaze-evoked nystagmus and downbeat nystagmus, was higher in SCA patients than that in normal subjects. Since SCA patients showed low scores despite wide visual scanning, the scanned area is considered to be abnormally enlarged. The larger scanned area in SCA patients was supposed mainly to result from the slightly larger saccade amplitude. Additionally, SCA patients showed prominent fixation disturbances probably due to gaze-evoked nystagmus and downbeat nystagmus. Consequently, SCA patients suffer from recognizing various objects in daily life, probably due to the impaired saccade control and impaired fixation.

Keywords Spinocerebellar degeneration · Vision · Eye movement · Saccade · Visual memory

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Introduction

It is widely believed that the cerebellum is intimately involved in coordinating skilled motor behavior, and impairment of the cerebellum is associated with the cerebellar motor symptoms such as cerebellar ataxic movements, e.g., dysmetria. However, recent studies have also discussed the role of the cerebellum in various cognitive functions. A neuropsychological study focused on cognitive and affective disturbances following focal primary cerebellar damage with common disturbances of attention, executive functioning, and frontal lobe-like behavioral and affective alterations [1], presumably caused by the cerebellar connections with the cerebral cortex [2–5], hence the term "dysmetria of cognition" [6–8].

Aside from somatomotor dysfunction, oculomotor control is also affected in cerebellar dysfunction. Cerebellar patients often present with a variety of oculomotor disorders such as saccadic dysmetria, gaze-evoked nystagmus, downbeat nystagmus, and square wave jerks [9–12]. Here, we hypothesized that cerebellar patients show the impairments in visual scanning due not only to dysmetria of cognition but also to "dysmetria in oculomotor control." We hypothesized that they would scan a larger area in comparison with normal subjects when viewing visual images because of saccadic dysmetria and/or impaired ocular fixation. We addressed these questions by recording eye movements in patients with pure cerebellar ataxia during a visual memory task with an eye-tracking device and compared the results with those of healthy subjects. Among various types of spinocerebellar degeneration

(SCD), we focused our study on patients with spinocerebellar ataxia type 6 (SCA6) and spinocerebellar ataxia type 31 (SCA31) to reveal abnormal visual scanning behavior in cerebellar patients. Although these are different disorders in terms of genetic background, both types of SCA present with pure cerebellar ataxia and characterized neuropathologically by an almost exclusive cerebellar involvement, particularly the selective loss of the cerebellar Purkinje cells [13–16].

To characterize visual scanning in cerebellar patients, we compared the parameters of visual scanning between SCA patients and normal subjects while the subjects scanned the presented figures to memorize them: amplitude of saccades, coefficient of variation (CV) of saccade amplitude, number of saccades, duration of fixation, instability ratio of fixation, and scanned area. In particular, we investigated which visual scanning parameters influenced the scanned area. We also compared the regions of interest (ROIs) between two groups upon which the subjects most frequently fixated.

Table 1 Characteristics of SCA patients and normal subjects

	SCA patients	Normal subjects	*p*
N	19	19	
Male/Female	9:10	12:7	n.s.
Age (years)			
Mean (SD)	64.5 (11.8)	63.4 (11.9)	n.s.
MMSE			
Median (range)	29 (25–30)	29 (26-30)	n.s.
Duration of illness (years)			
Median (range)	9 (3–28)		
ICARS			
Median (range)	55 (5–73)		
Gaze-evoked nystagmus (n)	15		
Downbeat nystagmus (*n*)	11		
Square wave jerks (*n*)	0		

MMSE Mini-Mental Status Examination, *ICARS* International Cooperative Ataxia Rating Scale, *n.s.* not significant

Patients and Methods

Subjects

Nineteen nondemented SCD outpatients who presented with pure cerebellar ataxia and 19 age-matched healthy volunteers (hereafter, normal subjects) participated in this study. The 19 SCD patients were genetically confirmed, with 12 as SCA6 and 7 as SCA31. The Mini-Mental Status Examination (MMSE) [17] was used to exclude SCA patients with dementia, showing scores less than 24, from this study. International Cooperative Ataxia Rating Scale (ICARS) [18] was applied to evaluate cerebellar somatomotor dysfunction. The characteristics of the SCA patients and normal subjects are shown in Table 1. There were no statistically significant differences in gender, age, and MMSE between the two subject groups.

Written informed consent to participate in this study was obtained from all subjects. The procedure was approved by the Ethics Committee of The University of Tokyo, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Visual Scanning Analysis: Eye-Tracking Device

The experimental setting was similar to that of our previous study [19, 20]. Subjects were seated with steady head position maintained by chin and forehead rests. The EyeLink 1000 system (SR Research, Mississauga, Ontario, Canada) was used to acquire ocular fixation position data at a sampling rate of 1,000 Hz. Gaze data were acquired from the left eye. Tasks were created using the SR Research Experiment Builder version 1.5.58 software, and images were presented on a Dell E173FPb monitor at 60 Hz. The distance between the screen and the subject was kept at 50 cm, so that each image subtended a total visual angle of 38°×30°, with 0.85 cm on the screen corresponding to approximately 1° of visual angle. Prior to the experiments, the subjects performed a nine-point calibration procedure to map the ocular fixation position onto screen coordinates.

Behavioral Paradigm: Visual Memory Task

Every time a subject pushed the button connected to the eye-tracking device, a figure appeared on the monitor and remained there for 10 s. In order to keep the subject gazing at the figure, the subject was instructed to memorize it. After a 10-s memorization period, the subject was instructed to draw the remembered figure on a piece of blank paper placed on the desk in front of the subject. Four figures in total were presented: (1) a cube, (2) two overlapping pentagons, (3) a house, and (4) the Rey-Osterrieth complex figure. These figures were selected from the copying tasks of various psychological batteries: the Birmingham Object Recognition Battery (image 1) [21], the MMSE (image 2) [17], the Western Aphasia Battery (image 3) [22], and the Rey-Osterrieth complex figure (image 4) [23, 24]. Since these figures were used in our previous study [19], it also enabled us to characterize the differences in visual scanning between SCA and Parkinson's disease (PD).

Data Analysis and Statistical Assessment

Heat maps, or graphical color-coded maps showing the distribution of ocular fixation positions, were created for each image using SR Research Data Viewer version 1.3.137. One heat map per image was created for each group, yielding a

total of eight heat maps. To create a heat map, a two-dimensional Gaussian function was applied to each of the fixation points. The Gaussian center was located at the ocular fixation position, while the width of the Gaussian function was influenced by an adjustable sigma value (set at 0.8) in degrees of visual angle, and the height of the Gaussian function was weighted by the duration of individual fixations. After the above process was applied to all fixation points, these Gaussian functions were normalized and overlaid in a color-coded fashion onto the original image. Heat maps color-coded into red, yellow, and green according to the duration of fixation were overlaid onto each of the images. Longer fixations are shown in red and shorter fixations in green. The shortest durations (the lowest 5 percentile) were eliminated automatically as a default setting. The size of green regions was measured by enclosing the outline of the green regions and calculated using the histogram analysis function of Adobe Photoshop Elements 2.0 (Adobe Systems Incorporated, San Jose, CA, USA).

The total area scanned (%), mean amplitude of saccades (degrees), coefficient of variation (CV) of saccade amplitude, total number of saccades (n), mean duration of fixation (ms), and the instability ratio of fixation were also measured as visual scanning parameters. The scanned area was defined as the area enclosed by the outline connecting the outermost positions of ocular fixations (Fig. 1), which was calculated using the histogram analysis function of Adobe Photoshop Elements 2.0 (Adobe Systems Incorporated, San Jose, CA, USA) and expressed as a percentage of the rectangular background of image. The duration of fixation was calculated as the mean duration of individual ocular fixation measured from the end of one saccade to the beginning of the next saccade. Even though nystagmus occurs during visual scanning, the fast phase of nystagmus was recognized as the saccade, and the slow phase was recognized as fixation according to the default setting in eye-tracking device. Instability of gaze due to impaired ocular fixation was explained almost totally by the slow phase of nystagmus based on the inspection of the eye movement records. To measure the slow phase of nystagmus, the slow oculomotor movements ranging from 5° per second to 10° per second were measured according to previous studies [25, 26]. The eye movements less than 5° per second, mostly comprising flick, drift, microtremor, were too small to detect with the eye-tracking device. The ratio of gaze instability was defined as the total time occupied by the slow phase of nystagmus within the total duration of the record.

We performed the following statistical analyses: (1) To compare the performance on visual memory tasks between SCA patients and normal subjects, Mann-Whitney's U test was used. (2) To investigate the difference in visual scanning parameters between SCA patients and normal subjects, these parameters were analyzed using two-way repeated measures analysis of variance (ANOVA) with a within-subject factor: image complexity (four levels) and a between-subject factor: subject group (two levels, SCA patients-normal subjects). If necessary, the Greenhouse-Geisser correction was used to evaluate nonsphericity. (3) To investigate which visual scanning parameters influenced the extent of the scanned area, multiple linear regression analyses were performed for SCA patients and normal subjects. We took the scanned area as the outcome variable and the other visual scanning parameters as predictor variables. The coefficient of determination was expressed as R^2, and the partial regression coefficients of predictor variables were expressed as β. The p value from the t test for the regression slope of predictor variables was used to determine the probability of the analysis. (4) To investigate whether the pattern of visual scanning differed between SCA patients and normal subjects, we performed the following analyses: the region which normal subjects most frequently fixated on was selected as the ROI and sum of the fixation durations within each ROI (the dwell time) in each region was compared between SCA patients and normal subjects. The dwell time was measured automatically by the eye-tracking device. The unpaired t test was used for this analysis. p Values of less than 0.05 were considered significant. Statistical analysis was performed using the SPSS software package (ver. 16.0; SPSS Inc., Chicago, IL, USA).

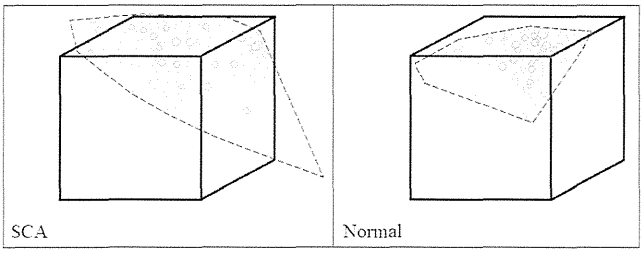

Fig. 1 Examples of scanned area analysis. The figures show the results of an ocular fixation analysis for an SCA patient and a normal subject while scanning image 1. The scanned area is defined as the ratio of the area enclosed by the outline of the ocular fixation positions (*gray shaded area*) to the area of the whole image

Results

Low Scores in Visual Memory Task in SCA

Figure 2 shows the representative results of the reproduced figures in an SCA patient and a normal subject. The percentages of completely reproduced figures were as follows: image 1, SCA 52.6 % (10/19), normal subjects 100.0 % (19/19), $p<0.001$; image 2, SCA 55.6 % (8/19), normal subjects 83.3 % (17/19), $p=0.002$; image 3, SCA 0.0 % (0/19), normal subjects 11.1 % (2/19), $p=0.297$; image 4, SCA 0.0 % (0/19), normal subjects 0.0 % (0/19), $p>0.999$.

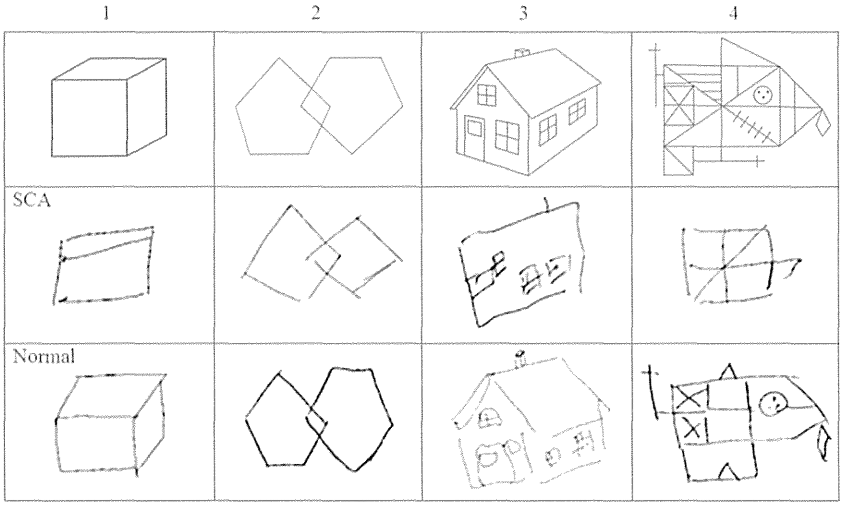

Fig. 2 Presented images and representative reproduced figures. *Image 1*—a cube; *image 2*—two overlapping pentagons; *image 3*—a house; *image 4*—the Rey-Osterrieth complex figure. The *upper panels* show the images presented to subjects. The *middle panels* show the figures reproduced by an SCA patient, and *lower panels* show those by a normal subject. In *image 1*, the SCA patient drew a two-dimensional figure, although the figure has some characteristic of a three-dimensional figure. Actually, approximately half of SCA patients failed to reproduce the figure, whereas all normal subjects were able to reproduce it. In *image 2*, the SCA patient incorrectly portrayed two overlapping squares instead of pentagons. Actually, more than half of SCA patients failed to reproduce the figure, whereas most normal subjects were able to reproduce it. In *images 3 and 4*, the reproduction scores in SCA patients were lower than those in normal subjects, although the differences were not statistically significant

Impairment of Visual Scanning in SCA

Figure 3 shows the heat maps. In all images, ocular fixation positions were distributed over a larger area in SCA patients than those in normal subjects. The green regions in SCA patients compared to those in normal patients were 125.8, 107.7, 117.7, and 105.7 % for images 1, 2, 3, and 4, respectively.

Figure 4 and Table 2 show the results of visual scanning parameters. The scanned area in SCA patients was significantly larger than that in normal subjects (Fig. 4a; tests of within-subject effects, image complexity×subject group interaction, $F_3=1.278$, $p=0.286$; tests of between-subject effects, $F_1=5.256$, $p=0.028$).

The amplitudes of saccades and CV were larger in SCA patients than those in normal subjects for almost all images, although the differences failed to reach statistical significance between the two groups (Fig. 4b; test of within-subject effect, image complexity×subject group interaction, $F_{2.276}=0.598$, $p=0.573$, and $\varepsilon=0.678$; tests of between-subject effect,

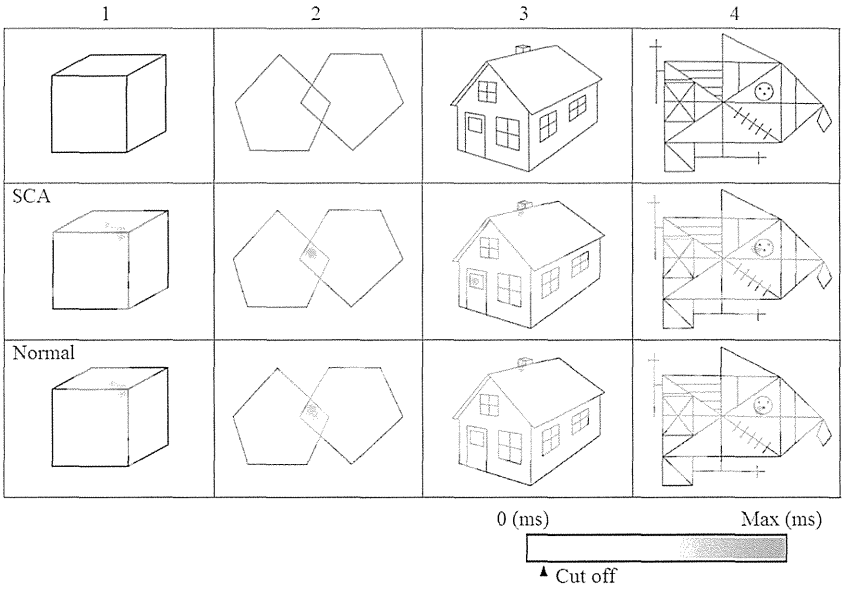

Fig. 3 Heat maps. The *upper panels* show the images presented to the subjects. The *middle panels* show the heat maps of the 19 SCA patients, and *lower panels* are those of the 19 normal subjects. In all images, the distributions of ocular fixation positions (*green regions*) in SCA patients were larger than those in normal subjects